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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/049,666
Filing Date: February 15, 2002
Appellant(s): SUZUKI ET AL.

Gregory T. Lowen
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5-14-10 appealing from the Office action mailed 9-23-09.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Proceedings

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 44-49

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

EP 0847 992	SUZUKI	6-1998
5,681,584	SAVASTANO	10-1997
5,500,422	ITO	3-1996

International Cosmetic Ingredient Dictionary and Handbook, 7th edition, pages 1617, 1637, 1653 (1997).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

REJECTION 1:

Claims 44-49 are rejected under 35 U.S.C. l03 (a) as being unpatentable over EP 0847 992 (Suzuki et al).

According to instant claims, the formulation of the benzamide derivative contain 1) an excipient which is either ***lactose, lactose anhydride, D-mannitol, corn starch and crystalline cellulose;*** 2) a lubricant selected from ***magnesium stearate, calcium stearate, stearic acid and talc;*** 3) a disintegrant which is either ***partly pregelatinized starch, Carmellose calcium and carboxy methyl starch sodium; 4) an amino compound or an inorganic base:*** The amino compound in turn could be either an ethanolamine or glycine, arginine or glutamate and the inorganic base is ***a carbonate , bicarbonate or disodium phosphate or sodium hydroxide.***

EP teaches benzamide derivative claimed by applicant (see claim 14). Additionally, EP teaches that the active ingredient may be used in general pharmaceutical compositions, and may be prepared with generally used diluents or excipients, such as binders, extenders, fillers, moisturizers, disintegrants, surfactants, and lubricants. EP also teaches that the pharmaceutical dosage form can be a tablet, pill, powder, solution, suspension, emulsion, granules, capsule, injection or suppository. More specifically, EP teaches the use of ***lactose (component 1), calcium carbonate***

(component 4) , amino acids, starch, methyl celluloses, ***calcium Carmellose (component 3)***, ***lactose***, sugars, ***stearates, talc (component 2) , polyethylene glycol***, sodium alginate and many other well known excipients (page 46, lines 5- 39). The selection of appropriate excipients in combination with claimed benzamide derivative would have been obvious to one of ordinary skill in the art with a reasonable expectation of success, since EP is suggestive of these art known excipients together with the benzamide derivative. The examiner also points out that in tablets routinely contain, binders, disintegrants, lubricants and buffering substances such as carbonates and bicarbonates and choosing the appropriate compounds falling under each category with a reasonable expectation of success would have been obvious to one of ordinary skill in the art at the time the invention was made.

REJECTION 2:

2. Claims 44-49 are rejected under 35 U.S.C. l03 (a) as being unpatentable over EP 0847 992 in view of the International Cosmetic Ingredient Dictionary and Handbook.

EP described above as teaching pharmaceutical compositions comprising benzamide derivatives. EP teaches the inclusion of many well-known pharmaceutical excipients. EP does not teach the inclusion of each of the specific excipients claimed by Applicant. EP does not specifically teach mannitol or claimed amino compound or organic and inorganic salts. The International Cosmetic Ingredient Dictionary and Handbook is relied upon for the teachings that mannitol as well known binder. Lastly, the Dictionary and Handbook is relied upon for the teaching that inorganic compounds

such as sodium bicarbonate, disodium phosphate, potassium bicarbonate and ammonia, as well as amino compounds such as triethanolamine, diethanolamine, diisopropanolamine, and triisopropanolamine, as well as organic acid salts such as sodium fumarate, and trisodium phosphate are all well known pH adjusters. Each of these types of excipients (binders, film formers and pH adjusters) is well known excipients used in the making of pharmaceutical formulations. Therefore, their inclusion in a pharmaceutical composition, which allows for necessary excipients, is not found to be patentable. The selection of a known material based on its suitability for its intended use is obvious, absent a clear showing of unexpected results attributable to the Applicant's specific selection. One skilled in the art would have been motivated to include the well-known excipients discussed above in the compositions described by EP with a reasonable expectation of success. The motivation to do so lies in the teaching of EP that well known excipients can be included in their formulation. Adjusting the pH of a composition is deemed to be within the skill of the art since that is routinely practiced in the fields of Chemistry and Biochemistry. The criticality of the product produced by dry granulation is unclear since one of ordinary skill in the art would avoid wet granulation process if the moisture leads to the degradation of the active agent. Therefore, this invention as a whole would have been prima-facie obvious to one of ordinary skill in the art at the time the invention was made.

REJECTION 3:

4. Claims 44-49 are rejected under 35 U.S.C. l03 (a) as being unpatentable over EP 0847 992 combination with Savastano (5,681,584).

The teachings of EP have been discussed above. EP does not specifically teach pregelatinized starch, mannitol, amino acids such as glycine, and inorganic salts such as disodium phosphate.

Savastano while disclosing tablet formulations of Benzamide derivatives suggests that excipients such as pregelatinized starch, mannitol, amino acids such as glycine, and inorganic salts such as disodium phosphate be used. Savastano further teaches that suitable tablet lubricants include calcium stearate, stearic acid and talk. (col. 7, line 4 through col. 8, line 65).

It would have been obvious to use these excipients in the compositions of EP would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since the reference of Savastano is suggestive of the use of these excipients with other benzamide derivatives. As pointed out above, adjusting the pH of the composition with acids and bases to obtain the desired pH at which the benzamide derivatives are fully active without degradation is well within the skill of the art. Furthermore, as pointed out above, tablets routinely contain, binders, disintegrants, lubricants and buffering substances such as carbonates and bicarbonates and choosing the appropriate compounds falling under each category with a reasonable expectation of success would have been obvious to one of ordinary skill in the art at the time the invention was made.

(10) Response to Argument

REJECTION 1: Appellant argues that Suzuki does not teach or suggest pharmaceutical formulation comprising a benzamide compound of the formula in combination with the specific additives as claimed in the independent claims 44 and 46. According to appellant Suzuki merely provides a generalized and undifferentiated list of additives such as those listed at page 46 and that without additional guidance, a person of ordinary skill in the art would not be motivated by the list of additives to prepare a particular formulations claimed.

These arguments have been fully considered, but are not found to be persuasive since in the tabletting art, the commonly used additives are a binder to bind the small amounts of the active agent, a disintegrants which enables the tablet to disintegrate in the system, a lubricant, amino compounds and buffering agents such as phosphates. What Suzuki advocates is the use of these in combination with the claimed benzamide derivatives. With regard to applicant's argument that without additional guidance, a person of ordinary skill in the art would not be motivated to prepare the particular formulations claimed by applicant, the examiner points out that instant claims do not recite specific combinations of compounds in specific amounts; In instant claims applicant only lists several compounds which belong to each category as binders, disintegrants etc as Markush members. Thus, the motivation comes from the tabletting art which uses the excipients, disintegrants, lubricants etc routinely. The examiner cites

(5,500,422) which shows the routinely used components in combination with benzamide compounds (see col. 10, line 60 through col. 11, line 4 and Example 68). With regard to the superior and unexpected properties with respect to the stability of the benzamide derivative against degradation argued by applicant (Table 1 in the brief), the examiner points out that the experiment was conducted with specific components with specific amounts whereas instant claims are drawn to the combination of several components. First of all, as pointed out before, instant 'benzamide derivatives' includes three different compounds and therefore, the results are not commensurate with the scope of the claims (even with regard to the amounts of the excipients). Secondly, each of (ii) and (iii) recite structurally unrelated components (art known excipients) the instant claimed combination of (ii) and (iii) would result in multitudes of combination products and applicants themselves have not shown the unexpected nature of the specific combination on the three different active agents claimed. Thirdly, as pointed out before, the examiner is unable to see how one can say that the differences observed are significant (no statistical evaluation was done), let alone ‘unexpected’. Appellant argues that samples outside the scope of claim 44, i.e., a, e, f and g do not contain an additional amino compound or inorganic base and for this reason, they are less stable than the samples b, c and d in that they result in a higher percentage of degradation products. These arguments are not persuasive since Suzuki does teach the inclusion of amino acids (instant claims recite arginine and glycine) and also quaternary ammonium base on page 46. The small increases in stability observed show only the proper pH

requirements of the compounds for their stability and it is a routine experimentation an artisan performs to obtain the best possible results.

Applicant's arguments to the above rejections based on the declaration by Masahiro Sakabe have been fully considered, but are not found to be persuasive. In his declaration, Masahiro Sakabe argues that he believes that an artisan skilled in the art of high-performance liquid chromatography (HPLC), the differences between the listed numbers are statistically significant. According to Sakabe Table 1 shows that when D-mannitol and compound I are mixed together and subjected to the indicated conditions, compound 1 is degraded by 0.21 percent (%) relative to the total amount of compound I present in the mixture and this value is comparable to the stability of compound 1 in the absence of any additional component (0.18 or 0.19 depending on the conditions tested). Further according to Sakabe in contrast, when lactose and compound I are mixed together and subjected to the indicated conditions, compound 1 is degraded by 0.55 percent (%) or 0.44 % relative to the total amount of compound 1 present in the mixture, depending on the particular conditions tested. Finally, Sakabe states that given his level of skill in HPLC chromatography, he believe that the difference between, for example, 0.21 (D-mannitol + compound 1) and 0.55 or 0.44 (lactose + compound 1) is statistically significant in that a conclusion may be drawn regarding the stabilizing effects of D-mannitol on compound 1 and the ***destabilizing*** effects of ***lactose*** on compound I. These arguments are not persuasive. The examiner is not questioning the level of skill of Masahiro Sakabe with regard to HPLC. What Masahiro Sakabe is offering is his opinion with regard to Statistics, which is totally different from HPLC results. Any data

obtained by any method or technique has to be analyzed statistically to evaluate the significance of the results. That means calculating the mean of a number of experiments and determine the standard deviation (or standard error) of the mean and analyze whether the differences observed between groups are statistically significant. Just looking at the data obtained and coming to a conclusion that the results are significant is deemed to be speculative. Furthermore, instant claims recite several members in each group of excipients, lubricants, disintegrants and inorganic base and the scope of the claims is not commensurate with the results obtained with lactose or mannitol. Finally it should be pointed out that the degradation values of the active agent observed with different excipients are so low and since the excipients, lubricants and disintegrants are known in tabletting technology and the prior is suggestive of these agents, selecting the proper excipient, lubricant, disintegrating agent and an inorganic base to obtain the best suited combination for that particular active agent is deemed to be within the skill of the art. With regard to the superior results with formulations b, c and d argued by applicant (Table 2 results), a careful examinations shows that these formulations contain in addition, a buffer ingredient (tris (hydroxymethyaminomethane, potassium bicarbonate and potassium carbonate respectively) and since a compound's ability to remain stable depends on the pH at which it is stable, selection of an appropriate buffering agent such as Tris, carbonates and bicarbonates would have been obvious to one of ordinary skill in the art. It is interesting to note that these formulations in Table 2 contain only polyethylene glycol and the inorganic bases, but none of the ingredients recited in the claims. Claims also do not recite polyethylene glycol. Furthermore, as pointed out

above, there is no evidence of statistical evaluation of the results indicating their significance. The examiner respectfully points out to the Board that instant claims recite "an excipient selected from the group consisting of lactose, lactose anhydride --------", the very compounds which appellant argues that ***degrade*** the benzamide compounds.

REJECTION 2: Appellant argues that the Dictionary and Handbook mechanically lists approximately 100 specific amino compounds, organic salts and inorganic salts, but does so under the general heading of 'pH adjusters' with no description of the suitability of one pH adjuster over another when combined with a benzamide compound such as those encompassed by appellant's claims 44 and 46. These arguments are not persuasive since adjusting the pH of a composition using suitable buffers or compounds is a routine experimentation practiced by an artisan in the highly developed field of biological sciences and tabletting industry.

REJECTION 3: Appellant argues that similar to Suzuki, Savastano contains undifferentiated lists of excipients. Appellant while admitting that Savastano does list mannitol as suitable additive argue that Savastano also lists lactose as a suitable additive in the same sentence and as observed by Appellants and as shown in Table 1 (at page 11 of Appellants' specification), lactose degrades a benzamide compound encompassed by Appellants' claims 44 and 46. Thus, Savastano cannot remedy the lack of teaching or suggestion in Suzuki regarding the destabilizing effects of various additives on benzamide compounds or the particular component requirements recited

by Appellants' claims 44 and 46. Further, there is no motivation provided by Suzuki for a person of ordinary skill in the art to focus on adding a narrowly defined class of non-disclosed additives (e.g., amino acids, mannitol and pregelatinized starch) to a formulation of a benzamide compound when literally over one hundred other excipients are taught in Savastano as equally suitable for inclusion in the described controlled release drag formulation. This argument is not persuasive since instant claims recite "an excipient selected from the group consisting of ***lactose, lactose anhydride*** --------", the very compounds which appellant argues that ***degrade the benzamide*** compounds.

Appellant argues that the dependent claims 45, 47, 48 and 49 are individually allowable at least because of their respective dependencies from independent claims 44 and 46. These arguments are not persuasive since mannitol and polyethylene glycol recited in these claims are known excipients and the same rationale as put forth above is still applicable. It should be noted that Suzuki teaches polyethylene glycol on page 46, line 30.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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